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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,627	10/08/2003	Carl H. June		7408

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,627	JUNE, CARL H.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-14* is/are pending in the application.

4a) Of the above claim(s) *10-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1 and 7-14 are currently pending. Claim 1 has been amended, and claims 48 and 49 have been cancelled by Applicants' amendment filed on 06-14-2010. Claims 10-14 were previously withdrawn form consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claims.

The terminal disclaimer filed on 06-14-2010 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the full statutory term of U.S. Patent No. 6,632,789 has been reviewed but has been unaccepted. The person who signed the terminal disclaimer, Tao Huang, does not have power of attorney, and thus, is not of record (see attached document DISQ.CKLIST copy attached hereto).

Therefore, claims 1 and 7-9 are currently under examination to which the following grounds of rejection are applicable.

Response to Applicants' arguments

Rejoinder

At page 4 of the remarks filed on 06-14-2010, Applicants point that claim 7 is a generic claim that links Groups I, II and III. Applicants request rejoinder of withdrawn claims 10-14 if claims 7 is found allowable. Because the claim 7 is not allowable as originally claimed, no other groups will be rejoined for search and examination at this point of prosecution.

Rejections/objections maintained in response to Applicants' arguments or amendments:

Claim Rejections - 35 USC § 112 - enablement

To the extent that claim 1 has been amended to broadly encompass a genus of agents that are not wortmannin wherein an agent inhibits phosphatidylinositol 3-kinase (e.g., activity or production) in a T-cell, wherein the agent inhibits IL-2 production *in vitro* by at least 50% when about 1nM to 100nM of said agent is applied to a T cell expressing a CD28 cell surface receptor that is stimulated by B7-1 or B7-2, wherein the agent inhibits *in vivo* T cell activation, the following rejection stands. Note that a T cell that is contacted with an agent that is not a wortmannin in a subject does not required to express a CD28 cell surface receptor that is stimulated by costimulatory molecules comprising B7-1, B7-2 or both.

Claim 1 remains rejected and claims 7-9 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **Rejection of claims 7-9 is necessitated by amendment of the claims in the response filed 06/14/2010.**

The instant claims are directed to a genus of agents able to inhibits PI 3-kinase in a T-cell, wherein said agents inhibit IL-2 production *in vitro* by at least 50% when about 1nM to 100nM of the agent contacts a T cell expressing a CD28 cell surface receptor that is stimulated by costimulatory molecules comprising B7-1, B7-2 or both, wherein said agent inhibits T cell activation *in vivo*.

While the specification clearly exemplifies the percent inhibition of IL-2 production in human T cells stimulated with anti-CD3 antibody (OKT3) and CHO cells expressing B7-1, B7-2

or both B7-1 and B7-2 by wortmannin (1 to 100 nM) in a dose-dependent manner (Fig. 3), the specification as filed is silent about other agents and their concentrations able to inhibit IL-2 at least 50% production by human T cells, wherein said agent inhibits intracellular production of PI 3-kinase in T-cell *in vitro*, thereby inhibiting T-cell activation *in vivo*. Figure 7A discloses two different concentration of wortmannin required to inhibit by at least 50% IL-2 production *in vitro* when T-cells are contacted either with B7-1 or B7-2 and anti-CD3+CHO, i.e., 100nM and 10nM, respectively. The 10-fold difference in concentration of Wortmannin-mediated inhibition of IL-2 production clearly indicates a dose-dependent response for at least 50% inhibition depending on specific costimulation of a T-cell. The specification is silent about concentrations required for at least 50% inhibition of other agent-mediated inhibition of IL-2 production, wherein said agent inhibits intracellular production of phosphatidylinositol 3-kinase in T-cell. Prior art exemplified by Bonjouklian (U.S. Patent No. 5,504,103, Date of Publication, April 2 1996, of record) provides further insight into the unpredictability of concentrations required for inhibition of PI 3-kinase in T-cell when it teaches *in vitro* testing of wortmannin analog β-hydroxywortmannin on bovine brain purified PI 3-kinase at 0.46 nM, e.g., IC_{50} of 0.2 ng/ml (col. 11, lines 65-66 bridging to col. 12, lines 1-5). The specification has not provided sufficient guidance for regions or domains of PI 3-kinase responsible for an agent-mediated inhibition of IL-2 production by at least 50% by T-cells or whether the agents effect intracellular production of PI 3-kinase in T-cell directly or indirectly. The specification merely discloses one example of an agent, i.e. wortmannin, which functions to inhibit intracellular PI 3-kinase in T-cells activated by anti-CD3 and the costimulatory molecules B7-1 or B7-2 resulting in Wortmannin-mediated inhibition of IL-2 production *in vitro* by at least 50% at 1nM to 100nM. No other working examples

demonstrating intracellular inhibition of PI 3-kinase in T-cells (e.g., activity or production) and agent-mediated inhibition of IL-2 production at 1nM to 100nM are disclosed. As an agent-mediated inhibition of IL-2 production by inhibiting intracellular PI 3-kinase in a T cell expressing a CD28 cell surface receptor with CHO cells transfected to express B7-2 or B7-1 is agent specific in a dose dependent manner, excessive trial and error experimentation would have been required to identify the necessary concentrations of about 1nM to 100nM characterizing the claimed genus of agents necessary to mediated inhibition of IL-2 production by inhibiting PI 3-kinase (e.g., activity or production) by at least 50%.

Response to Applicants' Arguments as they apply to rejection of Claims 1 and 7-9 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement

At page 4 of the remarks filed on 06-14-2010, Applicants essentially argue that claim 1 has been amended to recite the limitation suggested by the examiner, thus the rejection is moot. Such is not persuasive.

As the examiner suggested claim 1 has been amended to recite an agent-mediated inhibition of IL-2 production in a T cell expressing a CD28 surface receptor that is costimulated by B-7-1 or B7-2. However, Applicants have amended claim 1 to encompass a genus of agents that are not wortmannin able to inhibit production of PI 3-kinase in a T-cell, wherein said agents inhibit IL-2 production by at least 50% *in vitro* at concentrations of 1 nM to 100 mM. Applicants merely disclose one example of an agent, wortmannin, able to inhibit IL-2 production when a T-cell is stimulated by either B7-1 or B7-2 in conjunction with anti-CD3 antibody, wherein wortmannin is used at various concentrations (0-100 μM) resulting in Wortmannin-mediated inhibition of IL-2 production in a dose-dependent manner (Fig. 3).This is not sufficient, as the

ordinary artisan would immediately recognize that inhibition of an active or binding site in PI 3-kinase in a T-cell is dose-dependent based on the agent used that is not a wortmannin.

Rejection, Obviousness Type Double Patenting-

Claims 1 and 7-9 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789 for the reasons already of record as set forth in the office action of 12-12-2008.

The examiner refers Applicants to the reasons explained in the paragraph above.

Claim Rejections - 35 USC § 103

To the extent that claim 1 does not require for the claimed agent that is not a wortmannin able to inhibit IL-2 production *in vitro* by at least 50% when about 1nM to about 100nM of said agent is contacted to T cells to have the same *in vivo* disclosed IC_{50}, the following rejection stands. Note that a contacted T cell with an agent that is not a wortmannin in a subject does not required to express a CD28 cell surface receptor that is stimulated by costimulatory molecules comprising B7-1, B7-2 or both.

Claim 1 remains rejected and claims 7-9 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over by Bonjouklian ET al., (U.S. Patent No. 5,504,103, Date of Publication, April 2 1996) in view of Vitali et al., *(Int J Artif Organs* 1993 Dec;16 *Suppl* 5:196-200) and Bochner et al., (1994, *Ann. Rev Immunology,* pp. 295-335). **Rejection of claims 7-9 is necessitated by amendment of the claims in the response filed 06/14/2010.**

Bonjouklian et al., teaches *in vitro* testing of β-hydroxywortmannin, a wortmannin analog, on bovine brain purified phosphatidylinositol 3-kinase (PI 3-kinase). β-

hydroxywortmannin inhibits PI 3-kinase at concentration of 0.46 nM i.e., IC_{50} of 0.2 ng/ml (0.46 nM) (col. 11, lines 65-66 bridging to col. 12, lines 1-5). Because, contacting T cells *in vivo* with β-hydroxywortmannin does not require a particular IC_{50} concentration, hydroxywortmannin at 0.46 nM should reasonably be expected to inhibit phosphatidylinositol 3-kinase in any and all cells in mammals which express phosphatidylinositol 3-kinase after contacting T cells so as to inhibit T cell activation in a subject suffering from rheumatoid arthritis or allergy. Bonjouklian et al., do not expressly teach contacting T cells or specifically T cells which express a CD28 receptor and are costimulated by B7-1 and B7-2 with wortmannin. Bonjouklian et al., also do not expressly teach the modulation of T cell proliferation or modulation of lymphokine production. However, it is implicitly in the methods taught by Bonjouklian et al., that the administration of a wortmannin analogs to a mammal results in the inhibition of phosphatidylinositol 3-kinase in any and all cells in mammals which express phosphatidylinositol 3-kinase. T cells are abundantly present in mammals and inherently express phosphatidylinositol 3-kinase.

Response to Applicants' Arguments as they apply to rejection of Claims 1 and claims 7-9 under 35 USC § 103

Applicant essentially argue that : 1) neither Bonjouklian, Vitali, and Bochner alone or in combination teach or even hint at the following claimed aspect: "wherein the agent inhibits IL-2 production in vitro when said agent is applied to T cells that are stimulated by B7-1 or B7-2, 2) Applicant has amended claim 1 to incorporate the limitation of claim 49, and 3) as is acknowledged by the Examiner, claim 49 is not obvious in view of the cited art, neither is claim

1 that has now incorporated the limitation of claim 49. The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), Vitali and Bochner complement the teachings of Bonjouklian by evidencing that it is well established in the art to use anti inflammatory compounds in the treatment of RA and allergic asthma which reduce or inhibit cytokine.

Regarding 2) and 3), upon further considerations of the proposed claim amendment, and to the extent that the claimed invention does not requires the same *in vitro* and *in vivo* disclosed IC_{50}, there is no reason why β-hydroxywortmannin inhibiting *in vitro* PI 3-kinase at concentration of 0.46 nM could not be expected to inhibit T cell activation in a subject suffering from rheumatoid arthritis or allergy when contacting a T cell in said subject.

35 USC § 112- First paragraph- New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and claims 7-9 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by amendment of the claims in the response filed 06/14/2010. This is a New Matter rejection.**

Claim 1 has been amended to recite "an agent which inhibits phosphatidylinositol 3-kinase in the T-cell, wherein the agent is not a wortmannin, wherein the agent inhibits IL-2 production *in vitro* by at least 50% when about 1 nM to about 100 nM of said agent is applied to T cells that are stimulated by B7-1 or B7-2" . The specification discloses in FIG. 7B the percent of Wortmannin-mediated inhibition of IL-2 production *in vitro* at concentration of 1 to 100 nM in human T cells stimulated for 24 hours with anti-CD3 antibody (OKT3) together with CHO cells expressing B7-1, B7-2 or both B7-1 and B7-2. Thus the specific embodiments regarding the breadth of "the agent is not a wortmannin, wherein the agent inhibits IL-2 production *in vitro* by at least 50% when about 1 nM to about 100 nM of said agent is applied to T cells that are stimulated by B7-1 or B7-2" sets forth a new range not previously disclosed as a contemplated embodiment in the present specification, nor one that was readily known and used in the art at the time of filing. Thus is not clear that the Applicant was in possession of a genus of undefined of agents that are not wortmannin able to inhibit IL-2 production *in vitro* by at least 50% when about 1 nM to about 100 nM of said agent is applied to T cells that are stimulated by B7-1 or B7-2".

The MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of

the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" .

Response to Applicants' Arguments as they apply to rejection of Claims 1 and claims 7-9 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement

At pages 5 and 6 of the remarks, Applicants argue that the specification provides sufficient disclosure for a range of "1 nM to about 100nM in Example 5 and Figure 7B. Such is not persuasive.

Figure 7B evidences the fact that IL-2 production stimulated by PMA in T cell by a pathway that is independent of CD28-stimulation is not inhibited or reduced by an inhibitor of PI 3-kinase, e.g., wortmannin. No description or suggestion of other agent - mediated inhibition of IL-2 production that is not wortmannin *in vitro* at concentration of 1 to 100 nM in human T cells stimulated for 24 hours with anti-CD3 antibody (OKT3) together with CHO cells expressing B7-1, B7-2 or both B7-1 and B7-2 is disclosed. Example 5 discloses the wortmannin ID_{50} for inhibition of B7-1-mediated stimulation that was between 10 and 100 nM and the wortmannin ID_{50} for inhibition of B7-1-mediated stimulation was between 10 and 100 nM. Thus the specific embodiments regarding the breadth of an agent - mediated inhibition of IL-2 production that is not wortmannin *in vitro* at concentration of 1 to 100 nM in human T cells sets forth a new range

not previously disclosed as a contemplated embodiment in the present specification, nor one that was readily known and used in the art at the time of filing.

Conclusion

Claims 1 and 7-14 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

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